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(54) Title: A SOLUTION FOR ORAL ADMINISTRATION CONTAINING ICI 182,780

(57) Abstract

The invention concerns a pharmaceutical composition in the form of a solution formulation adapted for oral administration which comprises ICI 182,780, a pharmaceutically-acceptable oil, a pharmaceutically-acceptable lipophilic surfactant, a pharmaceutically-acceptable hydrophilic surfactant, and a pharmaceutically-acceptable water-miscible solvent, and the use of the composition on oral administration to a warm-blooded animal to produce an antioestrogenic effect.

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Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9524893 A	21-09-95	AU 1897495 A	03-10-95
		CA 2185347 A	21-09-95
		EP 0750495 A	02-01-97

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A SOLUTION FOR ORAL ADMINISTRATION CONTAINING ICI 182,780

The invention relates to a novel pharmaceutical composition, particularly to a pharmaceutical composition adapted for oral administration containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, and more particularly to a solution formulation containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol. The invention also relates to the use of the pharmaceutical composition of the invention for oral administration to a warm blooded animal to produce an antioestrogenic effect and to a method of producing an antioestrogenic effect by the oral administration of an effective amount of the pharmaceutical composition of the invention.

It is disclosed in European Patent Application No. 0 138 504 that certain steroid derivatives are effective antioestrogenic agents. The disclosure includes information relating to the preparation of the steroid derivatives of that invention. In particular there is the disclosure within Example 35 of the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, which compound is specifically named in Claim 4. It is also disclosed that the compounds of that invention may be provided for use in the form of a pharmaceutical composition comprising a steroid derivative of the invention together with a pharmaceutically-acceptable diluent or carrier. It is stated therein that the composition can be in a form suitable for oral or parenteral administration. For oral administration it is stated that a tablet or capsule containing the steroid derivative of the invention is particularly convenient. It is further stated therein that the tablet formulation can contain diluents, for example mannitol or maize starch, disintegrating agents, for example alginic acid, binding agents, for example methyl-cellulose, and lubricating agents, for example magnesium stearate. No pharmaceutically-acceptable diluent or carrier for a capsule formulation is specifically disclosed therein.

Subsequently the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol has been identified by the code number ICI 182,780 and that number shall be utilised for the compound hereinafter.

It is further disclosed in Cancer Research, 1991, 51, 3867-3873 and J. Endocrinology, 1992, 135. 239-247 that the antioestrogenic effect of ICI 182,780 in immature rats, mature rats or monkeys can be assessed by the administration of a suspension of the compound in arachis oil. This formulation was dosed either orally or by subcutaneous injection. The studies in rats demonstrated that the potency of the compound when dosed in arachis oil suspension was at least ten fold poorer when administration was by the oral route than when administration was by the subcutaneous route suggesting that the oral bioavailability of the compound from that formulation was low. A prolonged antioestrogenic effect was demonstrated when a dispersion of the compound in arachis oil was administered subcutaneously.

It is further disclosed in, for example, Laboratory Animal Science, 1993, 43, 247-251 that ICI 182,780 may be formulated for administration by intramuscular injection in a castor oil-based depot formulation. That formulation when given to laboratory animals at a dose of 4 milligrams per kilogram was found to inhibit the effects of endogenous oestrogen for three to four weeks.

Furthermore it is disclosed in J. Endocrinology, 1992, 135, 239-247, J. Endocrinology, 1993, 138, 203-209 and Cancer Research, 1994, 54, 408 that ICI 182,780 may be provided for administration by daily intramuscular injection in a 'short-acting' liquid formulation comprising ICI 182,780 in a propylene glycol-based solution.

It is an object of the present invention to provide a solution formulation containing the hydrophobic drug ICI 182,780 which does not exhibit, or which exhibits to a lesser degree, the problem of low oral bioavailability.

Many pharmaceutical compositions have been disclosed which are stated to be suitable for the dosing of hydrophobic drugs. Many of these formulations contain an oil such as arachis oil in which the hydrophobic drug is dissolved or dispersed. However the lack of miscibility of the oil with the aqueous environment of the gastrointestinal tract can lead to variable rates of absorption of the drug. To try to overcome the problem, it is common practice for a surfactant to be added to the pharmaceutical composition, particularly a hydrophilic surfactant such as a surfactant with a hydrophilic-lipophilic balance (HLB) of greater than about 8 and less than about 30. Such a surfactant may

produce an emulsion which, if the particle size is small, may lead to more complete absorption of the hydrophobic drug. However the use of hydrophilic surfactants may give a formulation of poor homogeneity as the surfactant may not be sufficiently miscible with the oil in which the hydrophobic drug is dissolved or dispersed. In a further refinement of such hydrophilic surfactant formulations, it is known that a lipophilic surfactant may be added to try to obtain the desired balance of hydrophilic and hydrophobic components to provide a stable emulsion when the formulation is added to an aqueous environment. The problem with this approach is that for each hydrophobic drug more than routine skill and knowledge is required to identify the exquisite balance of lipophilic and hydrophobic components which will provide a pharmaceutical composition of that hydrophobic drug which can be dosed orally to provide a reasonable oral bioavailability.

The many and various pharmaceutical compositions of the hydrophobic drug cyclosporin illustrate the complexities in this field of pharmaceutical research.

Thus, for example, it is disclosed in UK Patent Application No. 2 222 770 that cyclosporin may be formulated in a mixture of an oil such as a medium chain fatty acid triglyceride, a hydrophilic phase such as a mono- or di-alkyl ether of a polyoxyalkanediol, and a surfactant such as a hydrophilic or lipophilic surfactant or mixtures thereof.

Further it is disclosed in UK Patent Application No. 2 257 359 that cyclosporin may be formulated in a mixture of an oil such as a mixture of mono-, di- and tri-glycerides, a hydrophilic surfactant such as a surfactant having a HLB of at least 10, and the hydrophilic solvent 1,2-propylene glycol.

In addition it is disclosed in UK Patent Application No. 2 228 198 that cyclosporin may be formulated in a mixture of an oil such as a fatty acid triglyceride, a lipophilic surfactant such as a glycerol fatty acid partial ester, and a hydrophilic surfactant having a HLB of at least 10.

It has also been disclosed in PCT Patent Application WO 95/24893 that a hydrophobic drug may, for example, be formulated in a mixture of an oil such as a complete or partial ester of a medium chain or long chain fatty acid with a low molecular weight mono-, di- or polyhydric alcohol (for example a vegetable oil), a lipophilic surfactant such as a fatty acid or a mono- or di-glyceride of a fatty acid, and a hydrophilic surfactant having a HLB of greater than 10.

While this prior art shows some promising results, it should be recognised that ICI 182,780 is not a cyclic peptide like cyclosporin. ICI 182,780 is also a compound of higher molecular weight (Mol. Wt. = 603) and lipophilicity (estimated log P = 8 approx.) than the many drugs listed in PCT Patent Application WO 95/24893. Accordingly a pharmaceutical composition of ICI 182,780 is not disclosed in this prior art, nor can such a formulation be directly or unambiguously identified from consideration of this prior art.

We have investigated the factors which influence the solubilisation of ICI 182,780 and the maintenance of the compound in an absorbable form when it is dosed orally. We have developed solvents and mixtures of solvents which effectively solubilise the compound and we have also identified those oils and surfactants which facilitate the presentation of the compound in a suitable emulsion form to allow the enhanced absorption of the compound. We have discovered that surprisingly the selection and combination of particular classes of ingredients from within the formulations of known hydrophobic drugs provides the desired increase in oral bioavailability.

According to the invention there is provided a pharmaceutical composition in the form of a solution formulation adapted for oral administration which comprises:-

(i) ICI 182,780;

(ii) a pharmaceutically-acceptable oil;

(iii) a pharmaceutically-acceptable lipophilic surfactant;

(iv) a pharmaceutically-acceptable hydrophilic surfactant; and

(v) a pharmaceutically-acceptable water-miscible solvent.

Suitable pharmaceutically-acceptable oils include, for example, medium or long chain (C6 to C22, preferably C12 to C20, more preferably C6 to C12) fatty acids and mono-, di- or tri-glycerides of such fatty acids and mixtures of said fatty acids and mono-, di- and tri-glycerides. Preferably the pharmaceutically-acceptable oil is a triglyceride of a C6 to C12 fatty acid or a diglyceride of a C14 to C20 fatty acid. Examples of preferred pharmaceutically-acceptable oils include vegetable oils such as soyabean oil, olive oil, arachis oil and coconut oil, fractionated vegetable oils such as fractionated coconut oil, and animal oils such as fish liver oil. Of these oils, fractionated coconut oil is more preferred.

Suitable fractionated coconut oils include, for example, those made available commercially under the trade name "Miglyol" from Huls (UK) Ltd., Milton Keynes, UK such as:-

Miglyol 810 which comprises a mixture of caprylic and capric acid triglycerides having an approximate fatty acid composition of C6 : 2%; C8 : 68%; C10 : 28% and C12 : 2%;

Miglyol 812 which comprises a mixture of caprylic and capric acid triglycerides having an approximate fatty acid composition of C6 : 3%; C8 : 56%; C10 : 36% and C12 : 5%; and

Miglyol 818 which comprises a mixture of caprylic, capric and linoleic acid triglycerides having an approximate fatty acid composition of C6 : 3%; C8 : 53%; C10 : 33%; C12 : 4% and C18 : 5%.

Of these fractionated coconut oils, Miglyol 812 is preferred.

Suitable pharmaceutically-acceptable lipophilic surfactants include, for example, surfactants with a hydrophilic-lipophilic balance (HLB) of less than about 10, for example fatty acids such as capric, caprylic, oleic and linoleic acid, and mono- or di-glycerides (or mixtures of mono- and di-glycerides) of fatty acids such as capric, caprylic and oleic acid, for example the lipophilic surfactants made available under the trade name "Imwitor" from Huls (UK) Ltd. such as Imwitor 988, Imwitor 742 and Imwitor 308 and those made available under the trade name "Capmul" from Karlshamns, Karlshamn, Sweden such as Capmul MCM.

Of these lipophilic surfactants, mixtures of the mono- and/or di-glycerides of capric and caprylic acids such as Imwitor 988 and Imwitor 742, especially Imwitor 988, are preferred.

Suitable pharmaceutically-acceptable hydrophilic surfactants include, for example, surfactants with a HLB of greater than about 10, for example the condensation products of an alkylene oxide such as ethylene oxide with castor oil or with hydrogenated castor oil, for example the hydrophilic surfactants made available under the trade name "Cremophor" from BASF, Cheadle Hulme, Cheshire, England such as Cremophor RH40, those made available under the trade name "Etocas" from Croda Chemicals, North

Humberside, England such as Etocas 40, and those made available under the trade name "Nikkol" from Nikko Chemicals Co. Ltd., Tokyo, Japan such as Nikkol HCO-60.

Of these hydrophilic surfactants, Cremophor RH40 is preferred.

Suitable pharmaceutically-acceptable water-miscible solvents include, for example, a (1-4C)alcohol such as ethanol and propanol, a poly-alcohol, for example, a monomeric poly-alcohol such as a (1-4C)alkylenepolyol, for example glycerol (propane-1,2,3-triol), or a (1-12C)glycol, for example ethylene glycol (ethane-1,2-diol), propylene glycol (propane-1,2-diol), diethylene glycol (3-oxapentane-1,5-diol), triethylene glycol (3,6-dioxaoctane-1,8-diol) and tetraethylene glycol (3,6,9-trioxaundecane-1,11-diol). Alternatively a suitable pharmaceutically-acceptable water-miscible solvent is, for example, a polymeric poly-alcohol such as polyethylene glycol (PEG), for example a PEG having an average molecular weight in the range 150 to 800 such as PEG 200, PEG 300, PEG 400 and PEG 600. Alternatively a suitable pharmaceutically-acceptable water-miscible solvent is, for example, an ether derivative of a pharmaceutically-acceptable poly-alcohol as defined hereinbefore, for example a mono-(1-4C)alkyl ether derivative such as a mono-methyl ether derivative or, for example a mono-cyclic ether derivative such as a furfurylmethyl, tetrahydrofurfurylmethyl or tetrahydropyranylmethyl ether derivative. Examples of such suitable etherified poly-alcohols include glycerol mono-methyl ether, ethylene glycol mono-methyl ether, propylene glycol mono-methyl ether, ethylene glycol mono-tetrahydrofurfurylmethyl ether, diethylene glycol mono-methyl ether, diethylene glycol mono-ethyl ether (ethyl digol), diethylene glycol mono-tetrahydrofurfurylmethyl ether (glycofurol), diethylene glycol mono-tetrahydropyranylmethyl ether, triethylene glycol mono-methyl ether, triethylene glycol mono-ethyl ether, triethylene glycol mono-tetrahydrofurfurylmethyl ether, tetraethylene glycol mono-methyl ether and tetraethylene glycol mono-tetrahydrofurfurylmethyl ether. A suitable pharmaceutically-acceptable water-miscible solvent includes a mixture of two or more of the above-mentioned suitable water-miscible solvents. Preferred pharmaceutically-acceptable water-miscible solvents include propylene glycol and ethyl digol. Preferably ethanol or propylene glycol, or a mixture of ethanol and propylene glycol is used.

In a further advantage of the invention, it has been determined that, surprisingly, the combination of the above-mentioned ingredients of the pharmaceutical composition of the invention in the correct ratios improves the desired increase in oral bioavailability. In the table below, the advantageous relative ratios (as percentages of the weight of the formulation) are disclosed:-

Component	Generally	Preferred	More Preferred	Further Preferred
ICI 182,780	1-20%	2-18%	5-15%	8-12%
oil	1-20%	2-18%	5-15%	5-15%
hydrophilic surfactant	5-45%	10-40%	20-30%	20-30%
lipophilic surfactant	15-70%	25-60%	35-50%	35-50%
water-miscible solvent	1-30%	2-28%	5-25%	8-16%

The solution formulation of the invention may be presented in a form suitable for oral administration, for example a unit dosage form may be metered onto a spoon of suitable size and administered by mouth. Alternatively the solution formulation may be encapsulated by methods well known to those skilled in the arts of pharmaceutical science, for example by encapsulation within a shell comprising a gelatin or starch capsule such as a hard gelatin or starch capsule or a soft gelatin capsule [which may be formed from gelatin, an appropriate plasticiser (such as glycerin and sorbitol) and water].

The compositions of the invention may be obtained using conventional pharmaceutically-acceptable diluents well known in the art such as colouring, sweetening, flavouring and/or preservative agents. In the case of a soft gelatin capsule said diluents may be present in the liquid solution formulation encapsulated within the gelatin capsule or alternatively they may be present within the gelatin shell of the capsule. Capsule forms of the invention may be coated or uncoated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case using conventional coating agents and procedures well known in the art.

The amount of active ingredient i.e. ICI 182,780, which is employed in a single dosage unit will necessarily vary depending on the host treated and the particular dosage

form employed. For example a solution formulation which is administered on a spoon will generally have a volume in the range, for example, 0.5 ml to 10 ml and will contain the active ingredient at a concentration in the range, for example, 5 mg/ml to 150 mg/ml, preferably in the range, for example, 20 mg/ml to 100 mg/ml. Alternatively a soft gelatin capsule having an internal volume of, for example, 0.5 ml, 1 ml, 2 ml, 3 ml or 5 ml may be employed and will contain the active ingredient at a concentration in the range, for example, 5 mg/ml to 150 mg/ml, preferably in the range, for example, 15 mg/ml to 120 mg/ml, more preferably 100 mg/ml.

The size of the dose of ICI 182,780 will naturally vary according to the nature and severity of the disease state being treated, and the age of the animal or patient being treated. In general ICI 182,780 will be administered so that a daily dose in the range, for example, 0.1 to 10 mg/kg body weight is received given, if required, in divided doses. Preferably a daily dose in the range, for example, 0.1 to 2 mg/kg body weight will be administered.

As stated previously it was disclosed in J. Endocrinology, 1992, 135, 239-247 and 1993, 138, 203-209 that ICI 182,780 may be formulated for administration by intramuscular injection as a solution formulation comprising ICI 182,780 in a propylene glycol-based solution. There was no disclosure therein of the dosing of that solution formulation by the oral route. The only specific disclosures of the administration of ICI 182,780 by the oral route were made in the first of the above-mentioned papers in J. Endocrinology and in Cancer Research, 1991, 51, 3867-3873 wherein the formulation comprised a suspension of the compound in arachis oil.

Thus according to this aspect of the invention there is provided the use of a solution formulation comprising:-

(i) ICI 182,780;

(ii) a pharmaceutically-acceptable oil;

(iii) a pharmaceutically-acceptable lipophilic surfactant;

(iv) a pharmaceutically-acceptable hydrophilic surfactant; and

(v) a pharmaceutically-acceptable water-miscible solvent;

in the manufacture of a medicament for oral administration to a warm-blooded animal to produce an antioestrogenic effect.

This aspect of the invention also includes a method of producing an antioestrogenic effect by the oral administration to a warm-blooded animal in need of such an effect of an effective amount of a solution formulation comprising:-

(i) ICI 182,780;

(ii) a pharmaceutically-acceptable oil;

(iii) a pharmaceutically-acceptable lipophilic surfactant;

(iv) a pharmaceutically-acceptable hydrophilic surfactant; and

(v) a pharmaceutically-acceptable water-miscible solvent.

In these aspects of the invention the weight ratios of the ingredients of the solution formulation are as defined hereinbefore. In addition the single dosage unit of the liquid solution formulation and the daily dosage rate are as defined hereinbefore.

The invention will now be illustrated in the following Examples which involve tests of the aqueous dispersion profiles and oral bioavailabilities of ICI 182,780 contained within various pharmaceutical formulations. In general the test procedures used were those described below:-

Test of Aqueous Dispersion Profiles

The aqueous dispersion profiles of the solution formulations of the invention were assessed using the following conventional procedure which was conducted at ambient temperature. An aliquot (0.2 ml of the formulations containing 2 g of ICI 182,780 per 100 ml and 0.04 ml of the formulation containing 10 g of ICI 182,780 per 100 ml) of each test formulation was added to an aqueous sodium chloride solution (0.154 M, 10 ml) in a vial. The vial was sealed with a cap and the contents were mixed by the repeated inversion of the vial. The dispersion of the formulation and/or the precipitation of the active ingredient of the formulation was assessed visually.

Test of Oral Bioavailability

The oral bioavailability of ICI 182,780 in the dog from various formulations of the compound was determined using the following method. Each test formulation was dosed to a group of five male beagle dogs, each weighing approximately 18 kg. Unless

otherwise stated the studies were carried out with the animals in a 'fasted' state, that is the animals were not fed later than 18 hours prior to the dosing of a test formulation and they were not fed until 5 or 6 hours after dosing. The formulation of Example 1 was dosed orally by gavage. Each of the other formulations was contained in a hard gelatin capsule (size 00) and dosed orally. In each case, water (approximately 150 ml) was dosed immediately thereafter by way of gavage. Blood samples were taken from an external jugular vein at various times up to 8 hours after dosing. The level of ICI 182,780 in each blood sample was determined using a conventional radioimmunoassay using an analogous procedure to that described in Cancer Research, 1994, 54, 408 {antibodies were obtained on administration to a group of sheep of a conjugate obtained by a mixed anhydride based coupling of 17β-(3-carboxypropionyloxy)-7α-[9-(4,4,5,5,5-pentafluoropentylthio)nonyl]-oestra-1,3,5(10)-triene-3-ol [obtained from 7α-[9-(4,4,5,5,5-pentafluoropentylthio)nonyl]oestra-1,3,5(10)-triene-3,17β-diol (Example 35 of European Patent Application No. 0 138 504) and succinic acid] and thyroglobulin}.

Using this methodology, the oral bioavailability of ICI 182,780 obtainable from each test formulation was assessed using the conventional parameters of maximum drug concentration [Cp (max)], the area under the graph of drug concentration versus time [AUC (0-8h)] and a percentage figure for the oral bioavailablity based on a comparison of the AUC results obtained for the test formulation and for a formulation which was dosed intramuscularly (IM) comprising:-

IM Formulation	% Weight in grams per ml
ICI 182,780	2.0
Ethanol	10.0
Water (Ph. Eur.)	8.0
poloxamer 407	1.0
propylene glycol (Ph. Eur.)	to 100%

The following calculation was carried out to determine the oral bioavailability:-

$$\% \text{ Oral Bioavailability} = \frac{\text{AUC (oral)} \times \text{Dose (IM)}}{\text{AUC (IM)} \times \text{Dose (oral)}} \times 100$$

Comparative Example 1

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a precipitate which was noted to aggregate over a period of about 10 minutes.

Ingredient	% weight (g per 100 ml)	Pharmacokinetic Parameter	
ICI 182,780	2.0	Dose	50 mg
ethanol	10.0	Cp (max)	13.3 ± 2.7 ng ml^{-1}
water	8.0	AUC (0 to 8 hours)	34.9 ± 6.3 ng h ml^{-1}
propylene glycol	to 100%	Bioavailability	1.1 %

Comparative Example 2

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a crude emulsion.

Ingredient	% weight (g per 100 ml)	Pharmacokinetic Parameter	
ICI 182,780	10.0	Dose	50 mg
ethanol	13.5	Cp (max)	14 ± 2 ng ml^{-1}
Imwitor 988	76.5	AUC (0 to 8 hours)	28 ± 5 ng h ml^{-1}
		Bioavailability	0.8 %

Comparative Example 3

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a hazy, opalescent mixture, the turbidity of which increased gradually.

Ingredient	% weight (g per 100 ml)	Pharmacokinetic Parameter	
ICI 182,780	10.0	Dose	50 mg
propylene glycol	10.0	Cp (max)	20 ± 4 ng ml^{-1}
Imwitor 988	80.0	AUC (0 to 8 hours)	51 ± 10 ng h ml^{-1}
		Bioavailability	1.5 %

Example 1

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a hazy, opalescent mixture, the turbidity of which increased gradually over a period of 8 hours. The formulation gave the pharmacokinetic parameters shown below when dosed orally to dogs.

Ingredient	% weight (g per 100 ml)	Pharmacokinetic Parameter	
ICI 182,780	10.0	Dose	50 mg
Imwitor 988	40.0		
Cremophor RH40	26.8	Cp (max)	83 ± 19 ng ml^{-1}
Miglyol 812	13.2	AUC (0 to 8 hours)	194 ± 34 ng h ml^{-1}
ethanol	10.0	Bioavailability	5.5 %

Example 2

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a hazy, opalescent mixture, the turbidity of which increased gradually over a period of 8 hours. The formulation gave the pharmacokinetic parameters shown below when dosed orally to dogs.

Ingredient	% weight (g per 100 ml)	Pharmacokinetic Parameter	
ICI 182,780	10.0	Dose	50 mg
Imwitor 988	45.9		
Cremophor RH40	22.95	Cp (max)	78 ± 17 ng ml^{-1}
Miglyol 812	7.65	AUC (0 to 8 hours)	193 ± 35 ng h ml^{-1}
propylene glycol	13.5	Bioavailability	5.4 %

Example 3

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a hazy, opalescent mixture, the turbidity of which increased gradually over a period of 8 hours. The formulation gave the pharmacokinetic parameters shown below when dosed orally to dogs.

Ingredient	% weight (g per 100 ml)	Pharmacokinetic Parameter	
ICI 182,780	10.0	Dose	50 mg
Imwitor 742	40.0		
Cremophor RH40	26.8	Cp (max)	80 ± 14 ng ml^{-1}
Miglyol 812	13.2	AUC (0 to 8 hours)	195 ± 26 ng h ml^{-1}
ethanol	10.0	Bioavailability	5.6 %

Example 4

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a hazy, opalescent mixture, the turbidity of which increased gradually over a period of 8 hours. The formulation gave the pharmacokinetic parameters shown below when dosed orally to dogs.

Ingredient	% weight (g per 100 ml)
ICI 182,780	10.0
Imwitor 988	37.4
Cremophor RH40	22.95
Miglyol 812	7.65
ethanol	7.0
propylene glycol	15.0

Pharmacokinetic Parameter	
Dose	50 mg
Cp (max)	83 ± 11 ng ml^{-1}
AUC (0 to 8 hours)	194 ± 24 ng h ml^{-1}
Bioavailability	5.6 %

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CLAIMS

1. A pharmaceutical composition in the form of a solution formulation adapted for oral administration which comprises:-

(i) ICI 182,780;

(ii) a pharmaceutically-acceptable oil;

(iii) a pharmaceutically-acceptable lipophilic surfactant;

(iv) a pharmaceutically-acceptable hydrophilic surfactant; and

(v) a pharmaceutically-acceptable water-miscible solvent.

2. A pharmaceutical composition as claimed in claim 1 wherein the pharmaceutically-acceptable oil is a triglyceride of a C6 to C12 fatty acid or a diglyceride of a C14 to C20 fatty acid.

3. A pharmaceutical composition as claimed in claim 1 wherein the pharmaceutically-acceptable oil is fractionated coconut oil.

4. A pharmaceutical composition as claimed in claim 1 wherein the pharmaceutically-acceptable lipophilic surfactant is a mixture of mono- and di-glycerides of capric and caprylic acids.

5. A pharmaceutical composition as claimed in claim 1 wherein the pharmaceutically-acceptable hydrophilic surfactant is the condensation product of ethylene oxide with castor oil or with hydrogenated castor oil.

6. A pharmaceutical composition as claimed in claim 1 wherein the pharmaceutically-acceptable water-miscible solvent is ethanol, propylene glycol, diethylene glycol mono-ethyl ether or diethylene glycol mono-tetrahydrofurfurylmethyl ether, or a mixture thereof.

7. A pharmaceutical composition as claimed in claim 1 wherein the relative ratios of the ingredients (as percentages of the weight of the formulation) are:-

ICI 182,780	2-18%
oil	2-18%
hydrophilic surfactant	10-40%
lipophilic surfactant	25-60%
water-miscible solvent	2-28%

8. A pharmaceutical composition as claimed in claim 1 wherein the relative ratios of the ingredients (as percentages of the weight of the formulation) are:-

ICI 182,780	5-15%
oil	5-15%
hydrophilic surfactant	20-30%
lipophilic surfactant	35-50%
water-miscible solvent	5-25%

9. A pharmaceutical composition as claimed in claim 1 wherein the relative ratios of the ingredients (as percentages of the weight of the formulation) are:-

ICI 182,780	8-12%
oil	5-15%
hydrophilic surfactant	20-30%
lipophilic surfactant	35-50%
water-miscible solvent	8-16%

10. The use of a pharmaceutical composition as claimed in any one of claims 1 to 9 in the manufacture of a medicament for oral administration to a warm-blooded animal to produce an antioestrogenic effect.

11. A method of producing an antioestrogenic effect by the oral administration to a warm-blooded animal in need of such an effect of an effective amount of a solution formulation as claimed in any one of claims 1 to 9.

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INTERNATIONAL SEARCH REPORT

Inc .tional Application No
PCT/GB 96/03022

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/565 A61K9/08 A61K47/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 24893 A (SCHERER LTD R P ;LACY JONATHAN ERNEST (GB); EMBLETON JONATHAN KENN) 21 September 1995 cited in the application * p.14,; p.17, l.24-p.19, l.4; p.24, l.13-18; p.28, l.9; claims 1-9 *	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 March 1997	26.03.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (- 31-70) 340-2040, Tx. 31 651 epo nl, Fax (- 31-70) 340-3016	Uiber, P

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